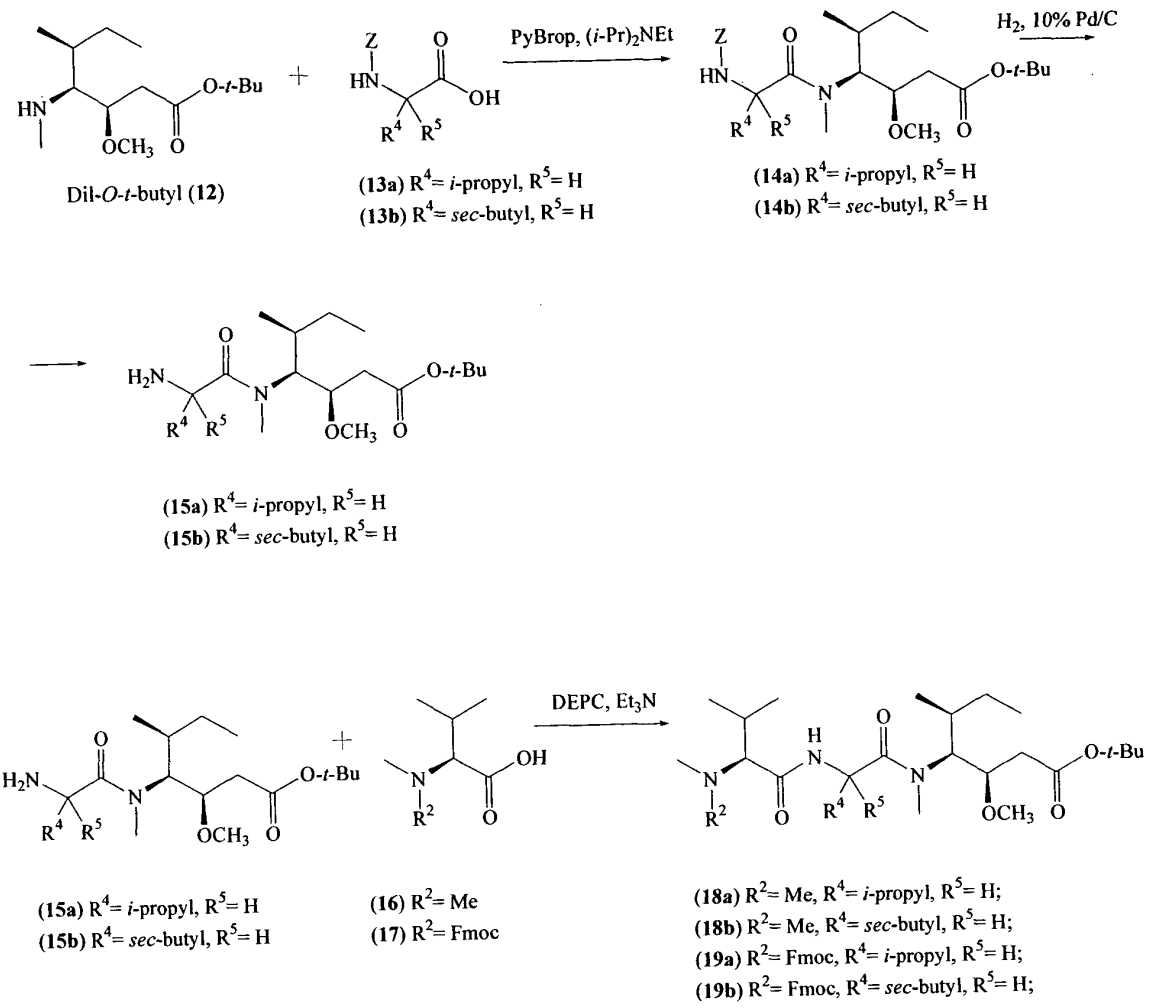
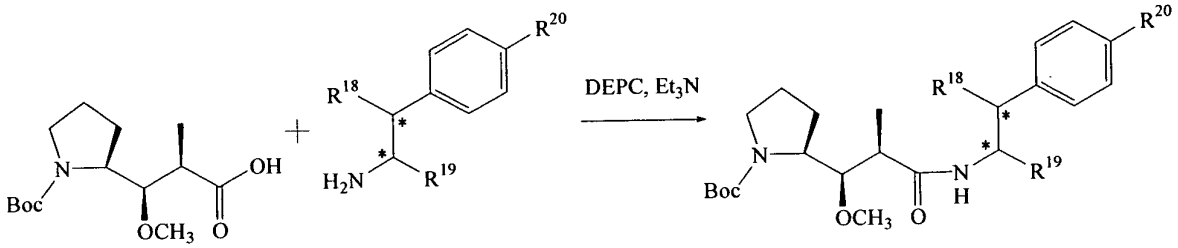

PyBrop, (i-Pr)2NEt
H2, 10% Pd/C
O-t-Bu
OCH3
Dil-O-t-butyl (12)
(13a) R4= i-propyl, R5= H
(13b) R4= sec-butyl, R5= H
(14a) R4= i-propyl, R5= H
(14b) R4= sec-butyl, R5= H
(15a) R4= i-propyl, R5= H
(15b) R4= sec-butyl, R5= H
DEPC, Et3N
(15a) R4= i-propyl, R5= H
(15b) R4= sec-butyl, R5= H
(16) R2= Me
(17) R2= Fmoc
(18a) R2= Me, R4= i-propyl, R5= H;
(18b) R2= Me, R4= sec-butyl, R5= H;
(19a) R2= Fmoc, R4= i-propyl, R5= H;
(19b) R2= Fmoc, R4= sec-butyl, R5= H;

Fig. 1

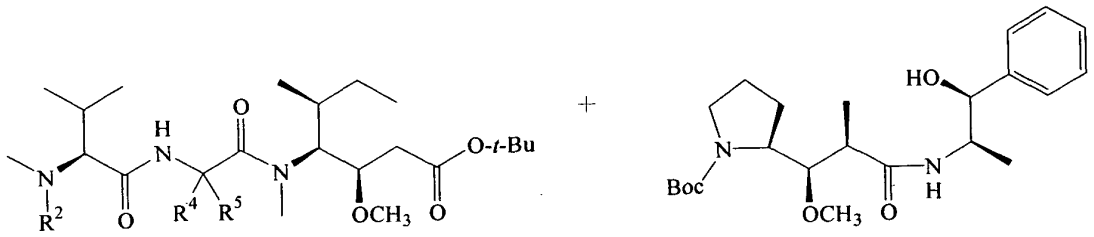


t-Boc Dolaproine (**20**)

(**21**) (1S,2R) R^{18}= OH, R^{19}= Me, R^{20}= H
(**22**) (S) R^{18}= H, R^{19}= CH_2OH, R^{20}= H
(**23**) (R) R^{18}= H, R^{19}= CH_2OH, R^{20}= H
(**24**) R^{18}= H, R^{19}= H, R^{20}= $C(O)CH_3$

(**25**) (1S, 2R) R^{18}= OH, R^{19}= Me, R^{20}= H
(**26**) (S) R^{18}= H, R^{19}= CH_2OH, R^{20}= H
(**27**) (R) R^{18}= H, R^{19}= CH_2OH, R^{20}= H
(**28**) R^{18}= H, R^{19}= H, R^{20}= $C(O)CH_3$

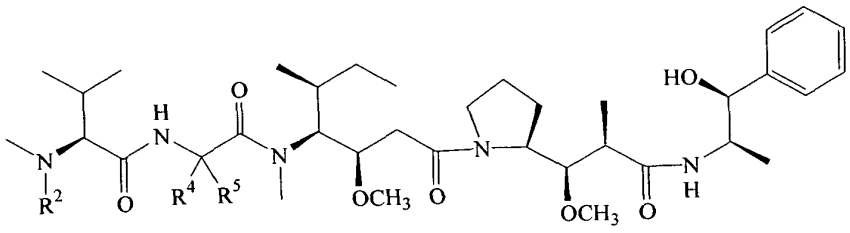
Fig. 2



(**18a**) R^2= Me, R^4= *i*-propyl, R^5= H;
(**18b**) R^2= Me, R^4= *sec*-butyl, R^5= H;
(**19a**) R^2= Fmoc, R^4= *i*-propyl, R^5= H;
(**19b**) R^2= Fmoc, R^4= *sec*-butyl, R^5= H;

(**25**)

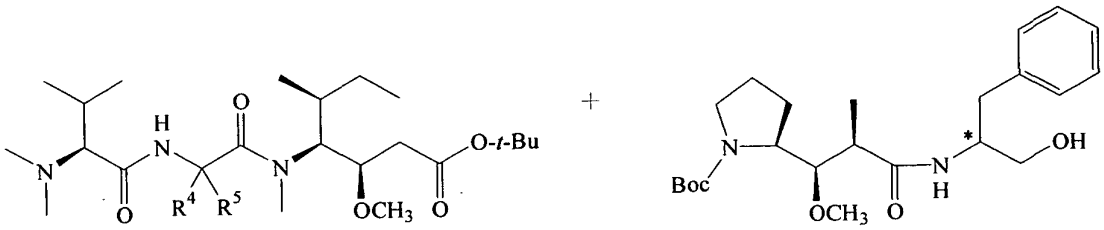
1. TFA/CH_2Cl_2
2. DEPC, Et_3N or,
   PyBrop, $EtN(i\text{-}Pr)_2$



(**29a**, auristatin E) R^2= Me, R^4= *i*-propyl, R^5= H;
(**29b**) R^2= Me, R^4= *sec*-butyl, R^5= H;
(**30a**) R^2= Fmoc, R^4= *i*-propyl, R^5= H;
- Fmoc → (**31a**) R^2= H, R^4= *i*-propyl, R^5= H;

(**30b**) R^2= Fmoc, R^4= *sec*-butyl, R^5= H;
- Fmoc → (**31b**) R^2= H, R^4= *sec*-butyl, R^5= H;

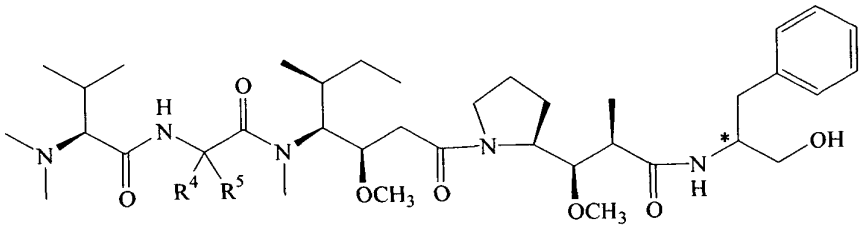
Fig. 3



(**18a**) R^4= *i*-propyl, R^5= H;

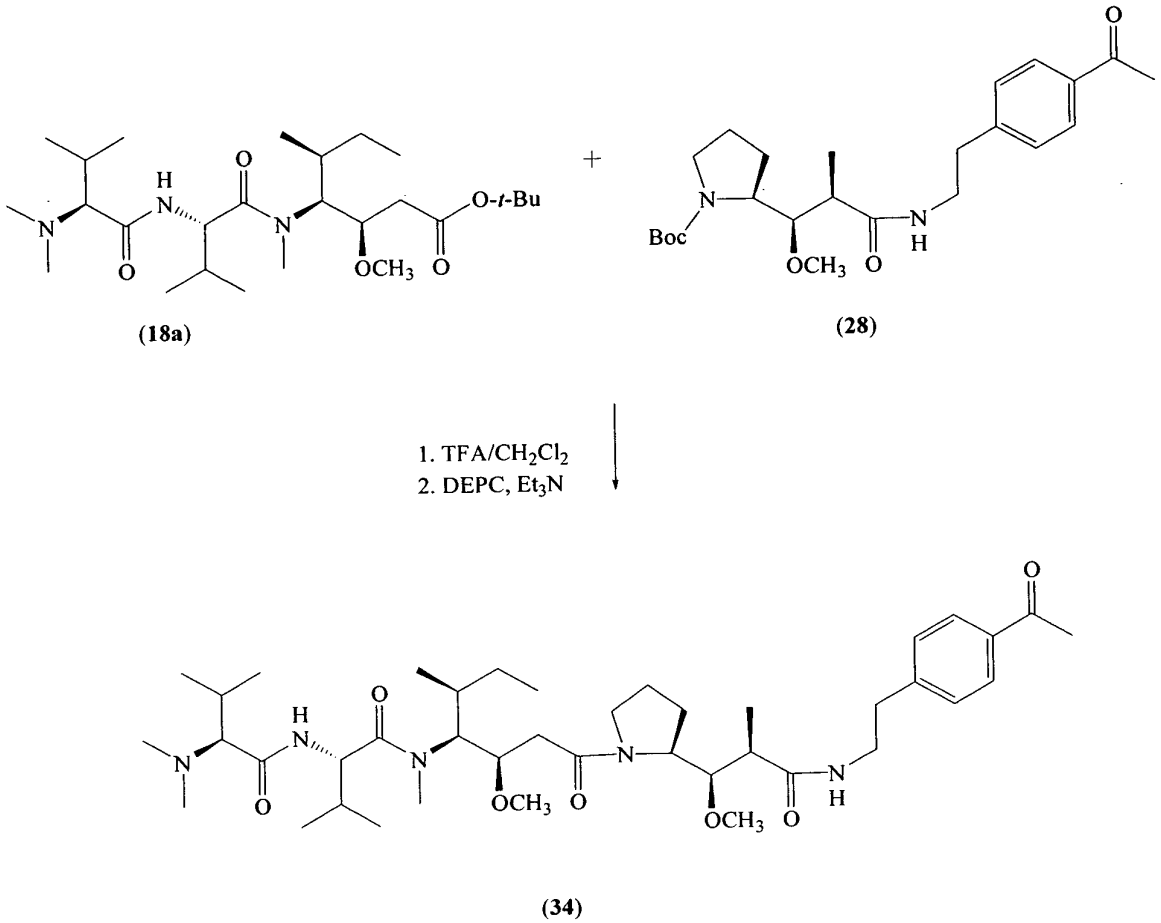
(**26**) (S)
(**27**) (R)

1. TFA/CH_2Cl_2
2. DEPC, Et_3N



(**32**) (S) R^4= *i*-propyl, R^5= H;
(**33**) (R) R^4= *i*-propyl, R^5= H;

Fig. 4



(18a)

(28)

(34)

Fig. 5

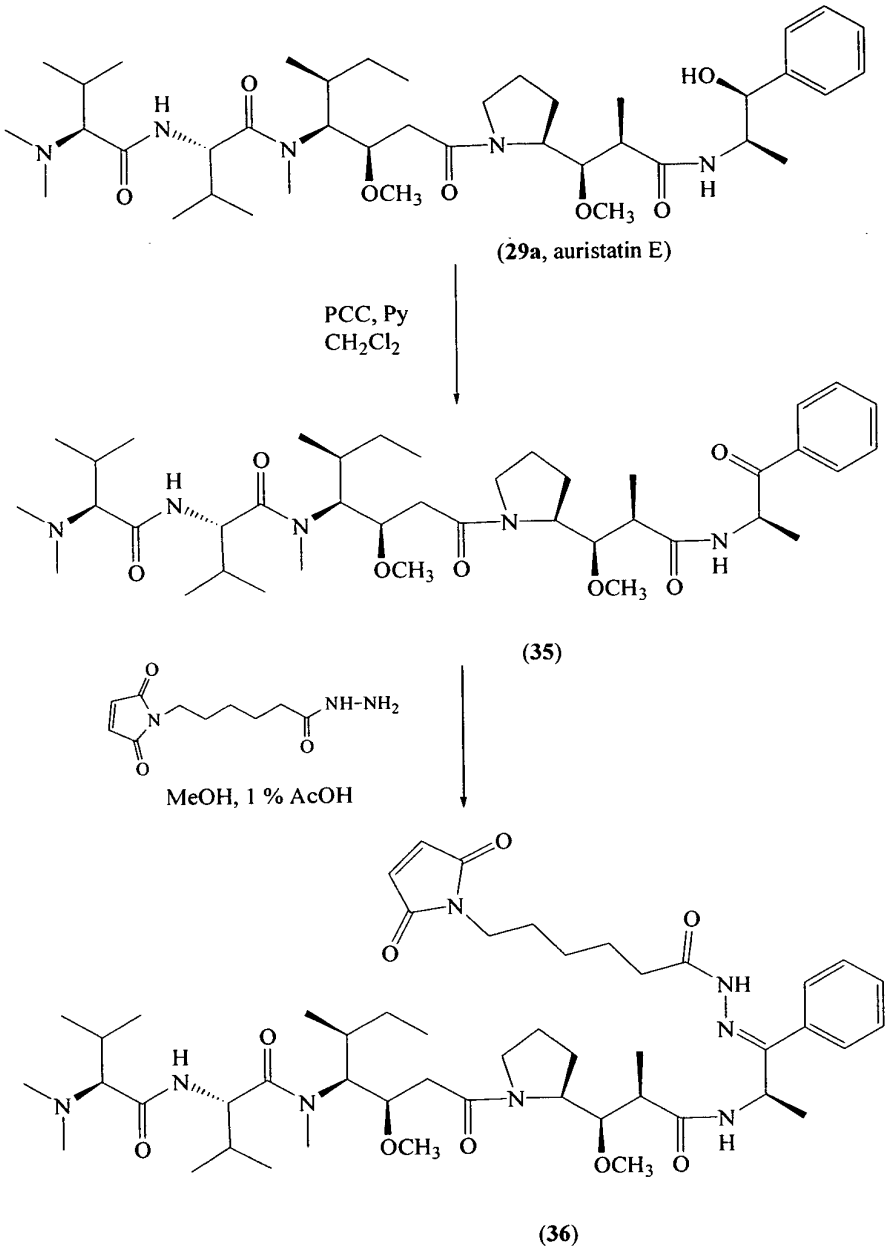


Fig. 6

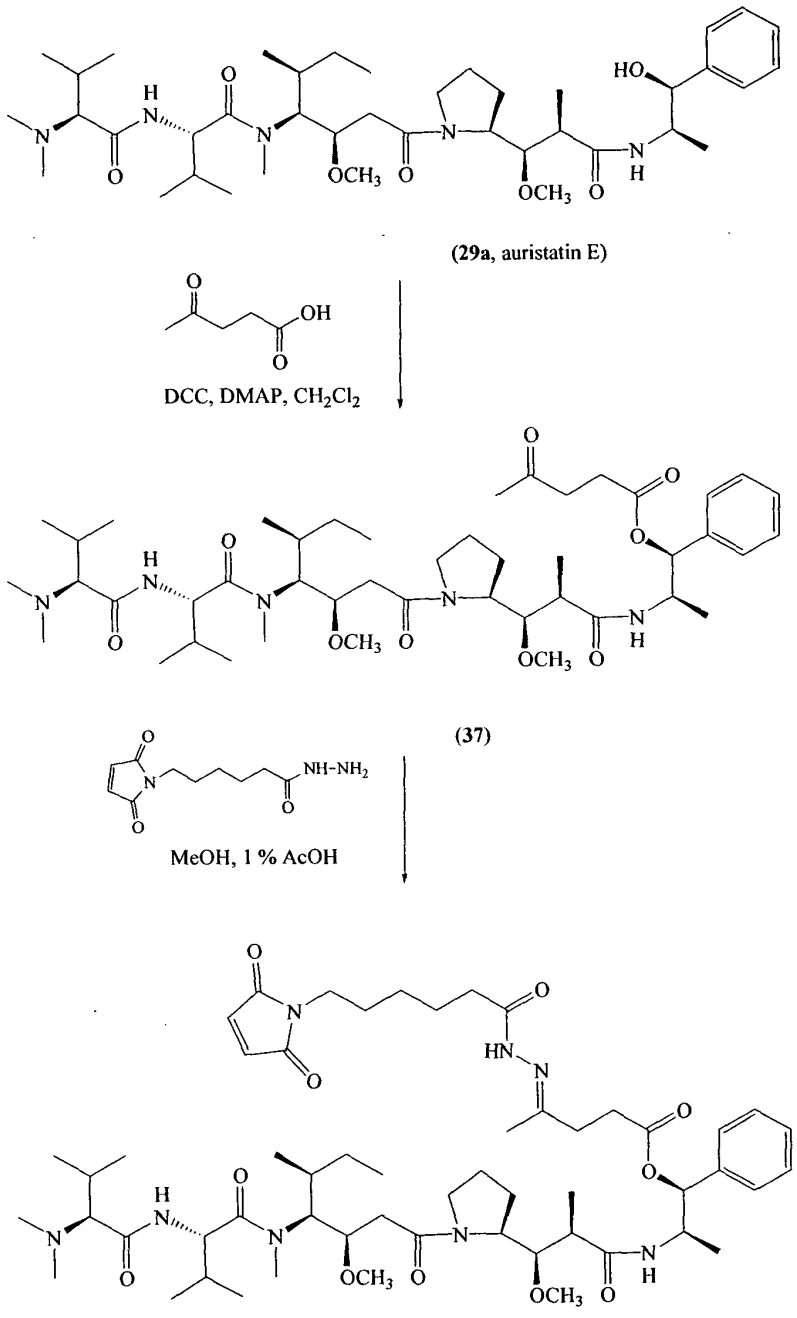
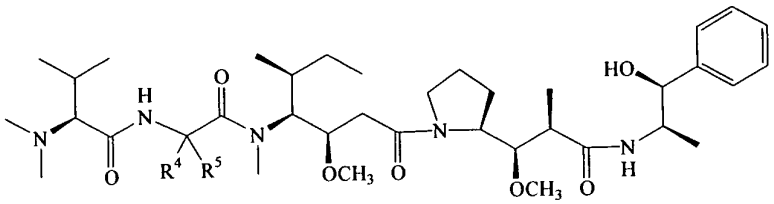
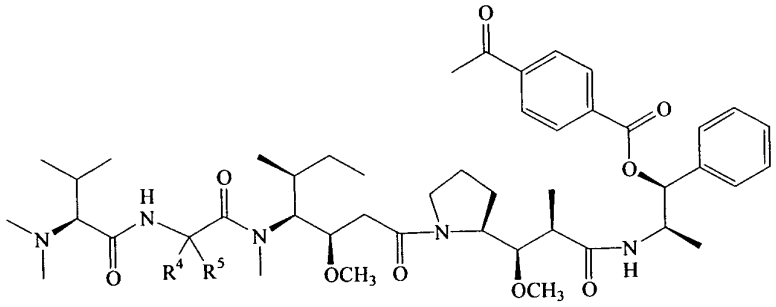


Fig. 7

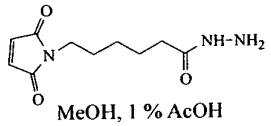


(**29a**, auristatin E) R^4= *i*-propyl, R^5= H;
(**29b**) R^4= *sec*-butyl, R^5= H;

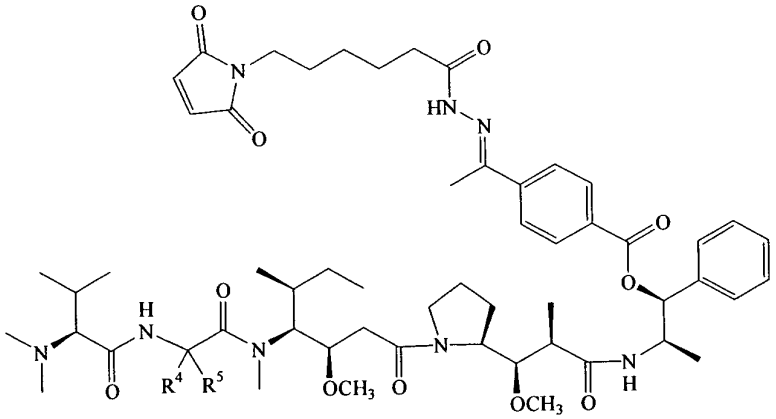
4-Acetobenzoic acid
DCC, DMAP, CH_2Cl_2



(**39a**) R^4= *i*-propyl, R^5= H;
(**39b**) R^4= *sec*-butyl, R^5= H;



MeOH, 1 % AcOH



(**40a**) R^4= *i*-propyl, R^5= H;
(**40b**) R^4= *sec*-butyl, R^5= H;

Fig. 8

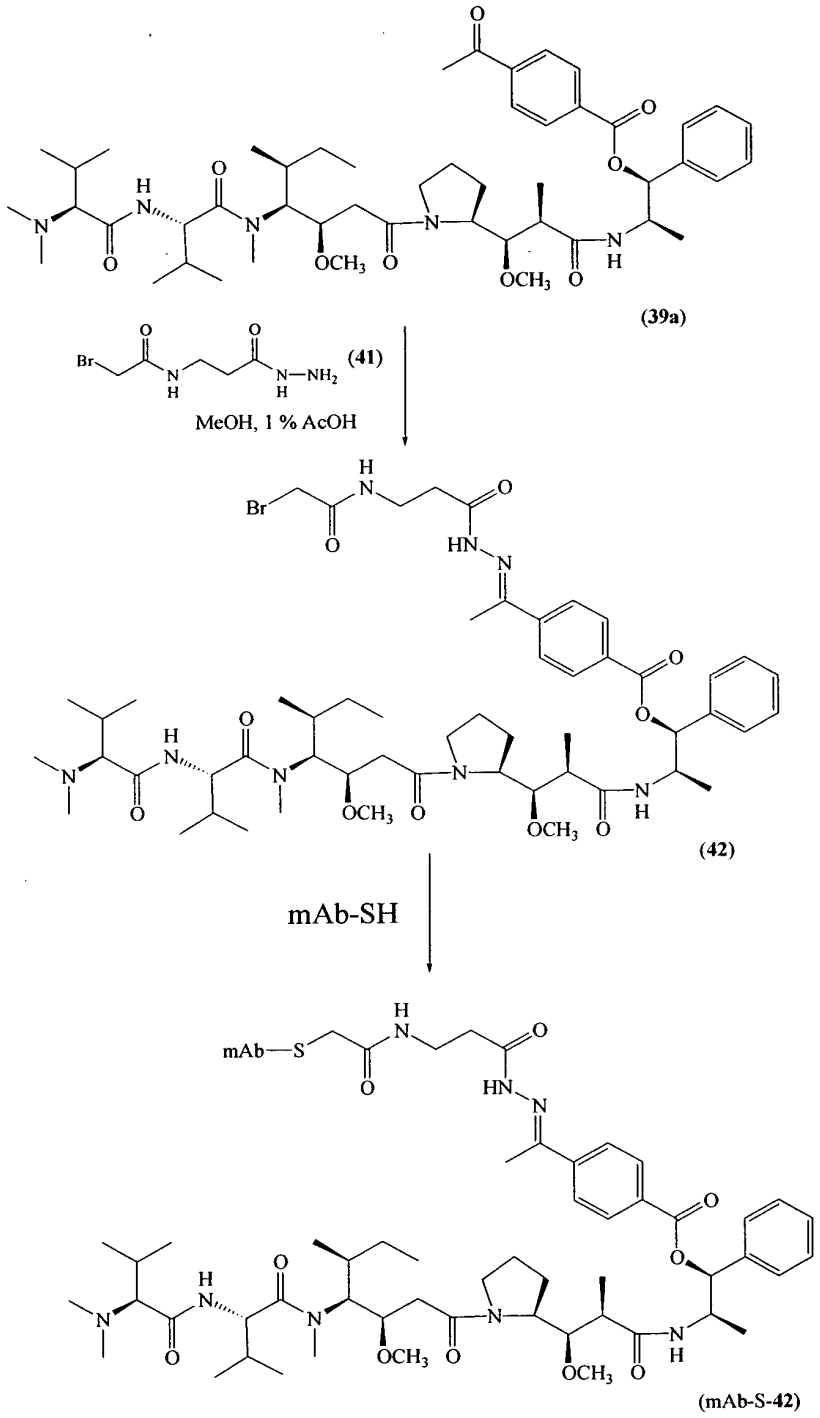
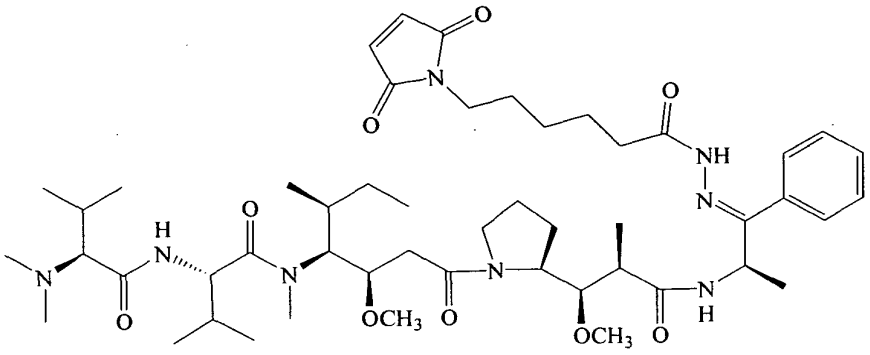
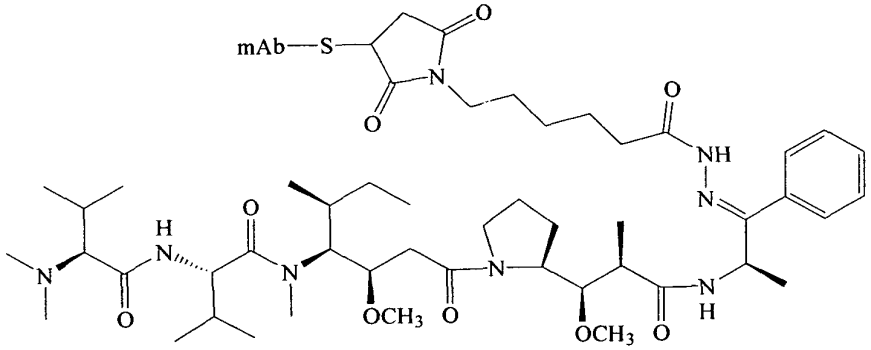


Fig. 9



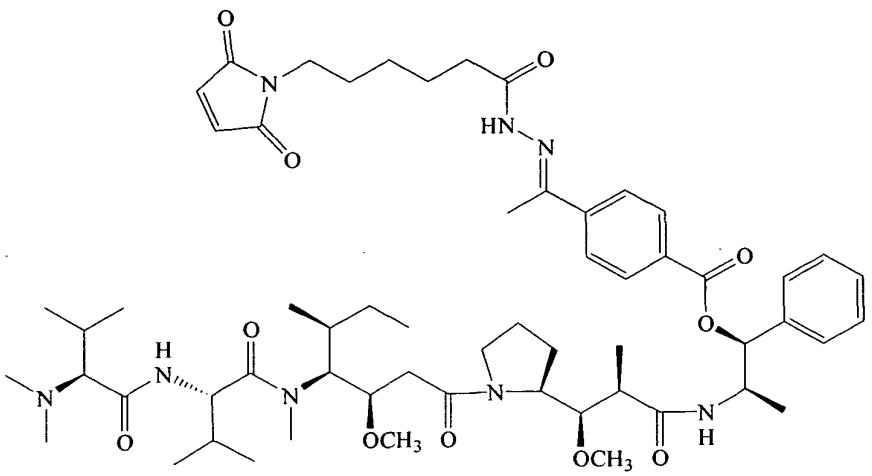
(36)

mAb-SH



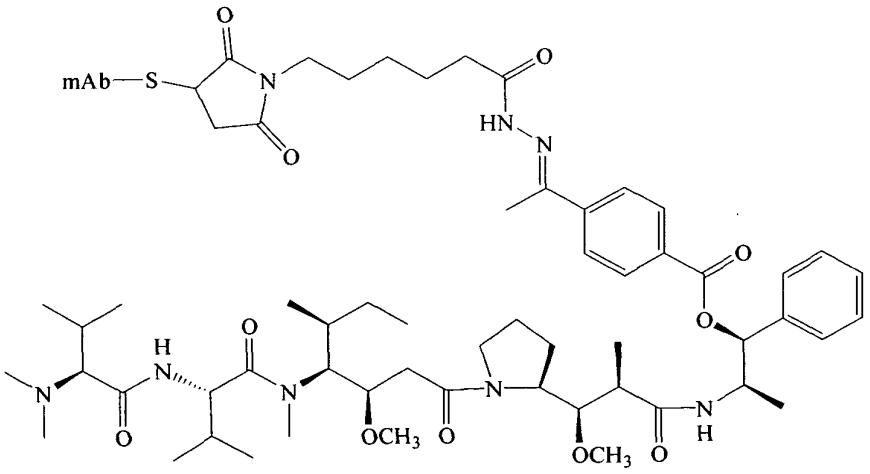
(mAb-S-36)

Fig. 10



(40a)

mAb-SH



(mAb-S-40a)

Fig. 11

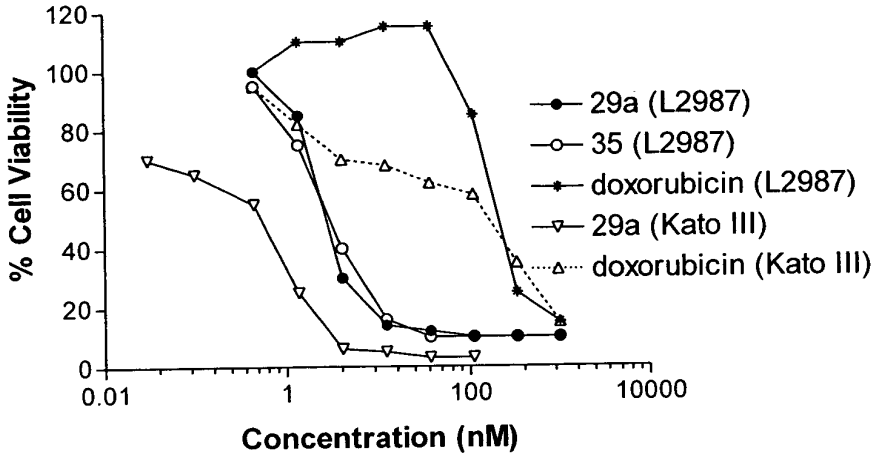


Fig. 12A

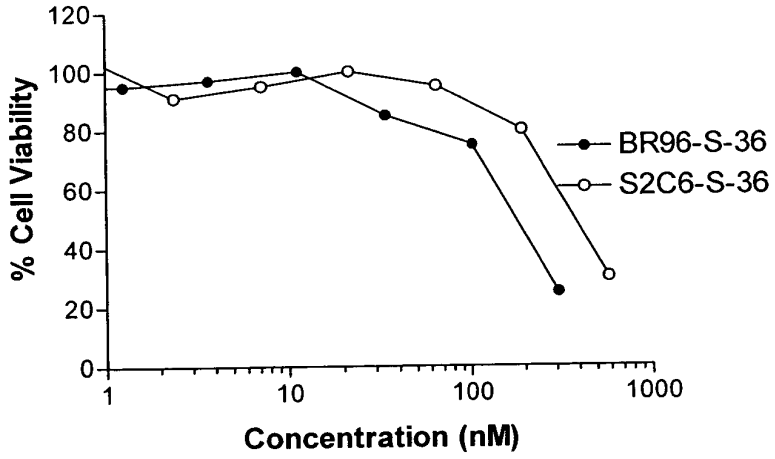


Fig. 12B

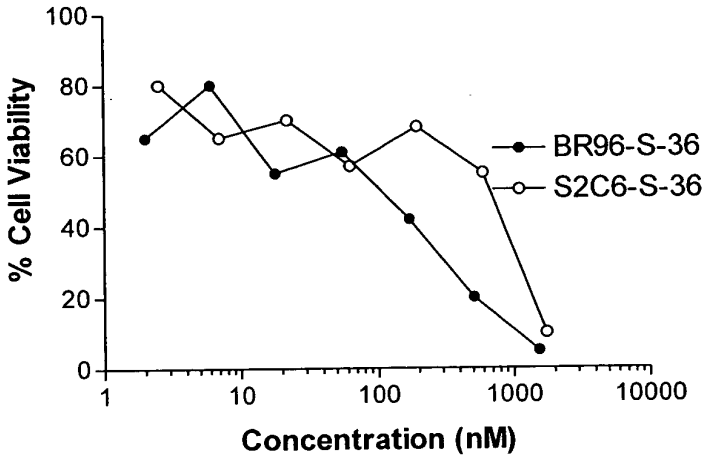

100
80
60
40
20
0
% Cell Viability
1
10
100
1000
10000
Concentration (nM)
BR96-S-36
S2C6-S-36

Fig. 12C

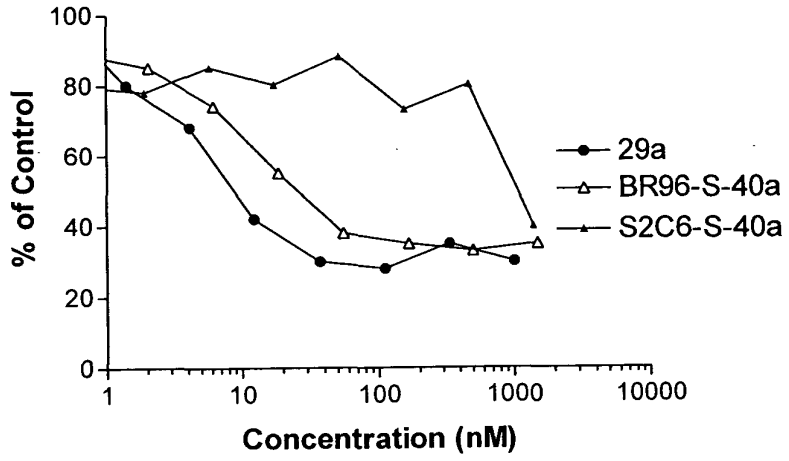


Fig. 13A

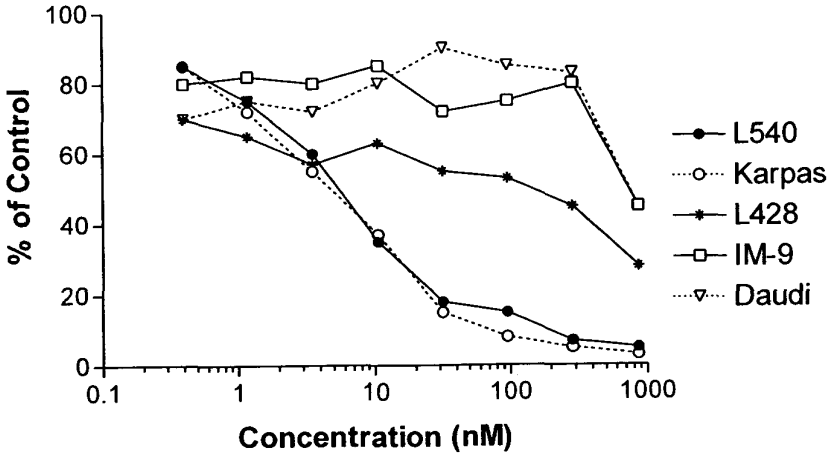


Fig. 13B

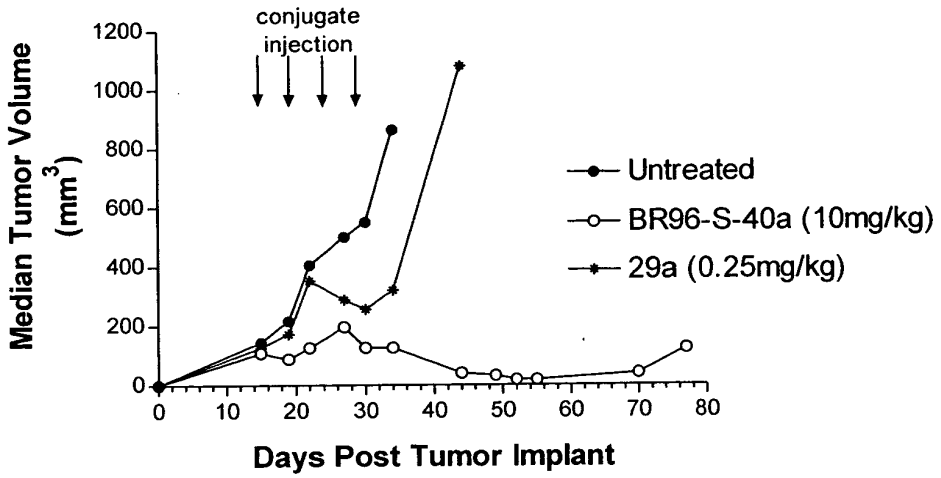


Fig. 14A

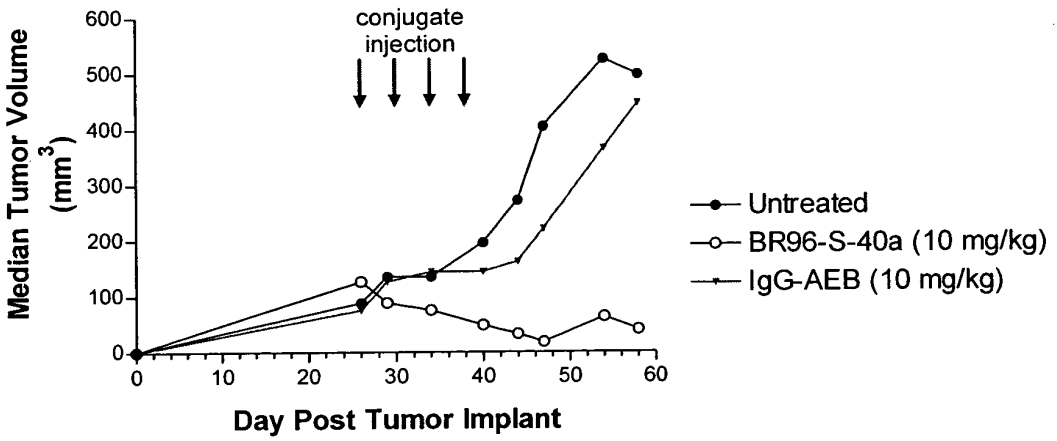


Fig. 14B